INFORMATION DISCLOSURE STATEMENTS

The PTO-1449 forms accompanying Information Disclosure Statements mailed on December 14, 1998 (4 pages) and May 6, 1999 (1 page) have not been initialed and returned to Applicants. In the Office Action dated February 25, 2000, the Examiner indicated on the Office Action Summary Sheet that Forms PTO-892 and PTO-1449 (paper numbers 5 and 7) were attached to the Office Action. These forms were not attached to the Office Action. The undersigned respectfully requests that copies of these forms be sent to the Applicants' representative.

This application as well as the parent applications recently have been assigned to Sequenom, Inc. A supplemental Information Disclosure Statement listing co-owned patent applications and patents as well as other citations is in preparation for filing under separate cover. Consequently, for example, U.S. Patent No. 5,547,835 and continuing applications, such as co-pending U.S. application Serial No. 08/467,208, which includes claims that read on primers and primers linked to solid supports, are now co-owned.

REJECTION OF CLAIMS 1-21 UNDER 35 U.S.C. §103(a)

Claims 1-21 are rejected under 35 USC § 103(a) as being unpatentable over Köster *et al.* (US 5,547,835) in view of Richards *et al.* (US 5,427,929) because Köster *et al.* teaches a nucleic acid sequencing method using mass spectrometry that uses a polymerase chain reaction to generate DNA fragments using a primer attached via the 5'-end through a spacer to a solid support, extraneous material is removed by washing, and the linker is cleaved at the 5' end, thereby releasing the DNA fragments when subjected to mass spectrometric analysis. The Examiner urges that Köster *et al.* teaches or suggests all aspects of the claimed primers except a primer with a chemically cleavable site at the 3'-end capable of being extended by an enzyme, or extension of the primer using a ligase enzyme. It is urged that Richards *et al.*, which allegedly teaches a method that employs ligase chain reaction and

polymerase chain reaction, and teaches a primer comprising a 3'-end cleavable site, cures these defects.

It is concluded that one of ordinary skill in the art at the time of the instant invention would have been motivated to have combined the references of Köster *et al.* and Richards *et al.* to make the claimed primers.

Relevant Law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir.

1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. In re Sernaker, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The Claims

Claim 1 and its dependents are directed to a primer comprising a 5'-end containing an immobilization site and a 3'-end that is capable of being extended by an enzyme and that contains chemically cleavable sites. The dependent claims specify various particulars, for example, claim 5 recites that the chemically cleavable site comprises a modified base, a modified sugar, or a chemically cleavable group incorporated into the phosphate backbone. Claim 7 recites that the chemically cleavable site is selected from the group consisting of dialkoxysilane, 3'-(S)-phosphorothioate, 5'-(S)-phosphorothioate, 3'-(N)-phosphoramidate, 5'-(N)-phosphoramidate, uracil, and ribose. Claims 9 and 10 recite that the enzyme used for extension of the primer of claim 1 may be DNA polymerase or ligase, respectively. Claim 12 recites that the immobilization attachment site is attached to an intervening spacer arm attached to the solid support. Claim 14 recites the types of materials that can be utilizes as a solid support, which may be functionalized to comprise avidin and/or streptavidin (claim 15) or an antibody (claim 16). The immobilization attachment site of the primer of claim 1 is a substituent on one of the bases or sugars of the primer (claim 18), biotin or digoxin (claim 19), or comprising a single-stranded nucleic

acid (claim 20). The primer of claim 20 further comprises a solid support, wherein the single-stranded nucleic acid is complementary to an intermediary oligonucleotide bound to the solid support and wherein the primer is attached to the solid support by hybridization (claim 21).

Differences Between the Teachings of the Cited References and the claims

Köster *et al.*

Köster *et al.* teaches methods for sequencing nucleic acids using mass spectrometry. The methods include using the Sanger sequencing strategy involving assembling the sequence information by analysis of the different molecular masses of the nested fragments that are obtained by base-specific chain termination. The teachings include introducing mass-modifications into the oligonucleotide primer, the chain-terminating nucleoside triphosphate, and/or in the chain-elongating nucleoside triphosphate and the use of tag-specific probes with mass differentiated molecular weights in order to increase throughput of the analysis method. Köster *et al.* teaches primers that include a linking functionality L at the 5'-end (which can include a spacer group). The reference teaches thio-modified phosphodiester or phosphotriester backbone modifications.

Köster *et al.* does not teach or suggest a primer with a 3'-end that contains a chemically cleavable site

Richards *et al.*

Richards *et al.* teaches a method for reducing carryover contamination in an amplification procedure by incorporating at least one modification into the amplification product to distinguish it from the target sequence for selective elimination. The reference teaches the inclusion of restriction endonuclease target sites as cleavable sites in the amplification products, and use of restriction endonucleases to cleave the resulting modified products (see, e.g., Figures 5-9, 12-15, 19). Prior to further amplification, the sample is treated to

selectively cleave the contaminant amplification product so that it cannot be amplified in the new sample.

The reference teaches a method of using ribonucleotide substitution in an amplification product so that it can no longer function as a template for amplification (col. 17, lines 33-45). This modified amplification product is then extended using PCR or LCR so that the ribonucleotide substitution is internalized in the sequence (col. 17, line 65 through col. 18, line 13). Richards *et al.* teaches incorporating chemically cleavable sites in the middle of an amplification probe or primer by synthesizing partial sequences containing amino groups on the 3'- or 5'-ends of the partial sequences and using DSP (dithiobis[succinimidyl-propionate]), DST (disuccinimidyl-tartarate), or EGS (ethylene glycol-bis-[succinimidyl]-succinate) to join together the 3'- and 5'-ends (col. 17, lines 1-18).

In particular, Richards *et al.* teaches that it is preferred to locate the chemically cleavable site modification near the middle of an amplification probe or primer so that disruption of hybridization will be minimized (col. 17, lines 19-22). Richards *et al.* states:

> It will be preferred to locate the chemically cleavable modification site near the middle of an amplification probe or primer so that disruption of hybridization will be minimized.

Thus, Richards *et al.* does not teach or suggest that the chemically cleavable site is in the 3'-end of the primer, or that is located within about five nucleotides from the 3'-end of the primer. The reference does not teach or suggest that the chemically cleavable site could be dialkoxysilane, 3'-(S)-phosphorothioate, 5'-(S)-phosphorothioate, 5'-(N)-phosphoramidate, or a modified sugar. Richards *et al.* does not teach or suggest a nucleic acid primer containing an immobilization attachment site or a solid support comprising an antibody.

Analysis

It is respectfully submitted that the Office has failed to set forth a *prima facie* case of obviousness.

(1) There would have been no motivation to have combined the teachings of Köster *et al.* with those of Richards *et al.*

The Examiner contends that one of ordinary skill in the art at the time of filing of the instant application would have been motivated to combine Köster *et al.* with Richards *et al.* and to make the primer as claimed because the primer of Köster *et al.* has a cleavable site with a disulfide bond modification to increase mass spectrometric performance (citing col. 13, lines 3-35), and Richards *et al.* teaches incorporating a chemical cleavage site into an amplified product at the 3'-end to produce an efficient and economical method for reducing carryover contamination in an amplification procedure (citing the Abstract).

Richards *et al.* teaches a method for reducing carryover contamination in an amplification procedure, a problem that is not present in the teachings of Köster *et al.* Richards *et al.* teaches using electrophoresis, radiolabeling and autoradiography for detection of the amplification products, where background contamination presents a significant problem. Köster *et al.* uses mass spectrometry for analysis, eliminating the need for electrophoresis.

Thus, the cited references are not directed to the same technology and, thus, would not have been combined. Furthermore, Köster *et al.* teaches the use of mass spectrometry for analysis, where generation of smaller fragmentation products of undesired amplification products by the method of Richards *et al.* would present more of a problem then the intact amplification product itself: larger fragments are more difficult to volatilize (Köster *et al.*, col. 6, lines 6-65) and therefore can be excluded from analysis. Therefore there would have been no motivation to have combined the teachings of these references, since the problem solved by Richards *et al.* is not a problem faced in mass spectrometric analyses.

Furthermore, neither Köster *et al.* nor Richards *et al.* suggests the desirability of the modification claimed in the instant application. The instant application teaches that a reason for incorporating a selectively cleavable site in the 3'-region of a primer permits cleavage of an extended product prior to nucleic acid sizing by mass spectrometry. This results in the reduction of the length of the nucleic acid of interest thereby advantageously extending the useful size analysis range (e.g., increased read lengths) for mass spectrometry analysis of nucleic acid by avoiding analysis of known sections of the nucleic acid contained in the cleaved primer sequence, and thereby increasing the efficiency of mass spectrometry analysis. Neither Richards *et al.* nor Köster *et al.* suggests reducing the length of the nucleic acid fragments prior to analysis. In fact, Richards *et al.* incorporates cleavable sites into nucleic acid molecules targeted for destruction, not analysis.

(2) Notwithstanding the lack of motivation, the combination of teachings of Köster *et al.* with the teachings of Richards *et al.* does not result in the instantly claimed nucleic acid primers.

The combination of Köster *et al.* and Richards *et al.* does not result in the instantly claimed subject matter.

The Office Action alleges that Köster *et al.* teaches nucleic acid primers containing 5'-region immobilization sites and incorporation of chemical cleavable sites into primers, but not in the 3'-region of the primer, and that Richards *et al.* cures this defect because Richards *et al.* teaches modification of an amplified product by incorporating a modified base into the primer prior to amplification. It is urged that combining Köster *et al.* with Richards *et al.* produces the primers of the instant application. Applicants respectfully disagree.

The Office Action urges that Richards *et al.* teaches incorporating a chemical cleavage site at the 3'-end of a primer (col. 16 line 65 through col. 17, line 5). It is respectfully submitted that this is incorrect. Richards *et al.* teaches modification at the 5'-end of one fragment and the 3'-end of another fragment and subsequently joining the fragments such that the chemically

cleavable site is near the middle of amplification probe or primer in order to minimize disruption of hybridization (col. 17, lines 19-22; and, e.g., Figure 10). Richards *et al.* states that for primers the modified site is "preferably placed at the 5'-end of the primer." Therefore Richards *et al.* does not teach or suggest a primer with a chemical cleavage site at the 3'-end. Instead, the chemical cleavage site of the primer of Richards *et al.* is near the middle of the amplification probe or primer. Thus, Richards *et al.* does not cure the deficiencies in the teachings of Köster *et al.*

Further, Richards *et al.* does not teach or suggest modification of the 3'-region of a primer in order to allow selective cleavage of the primer prior to analysis. Instead, Richards *et al.* teaches the incorporation of chemical cleavage sites in order to destroy the modified amplification product by treatment with reagent that cleaves the modification site (col. 16, 51-55, col. 17, lines 12-18). The cited references, either by themselves or in combination, do not teach or suggest every element of the claims of the instant application. Köster *et al.* does not teach or suggest using a nucleic acid primer that includes a 3'-end chemically cleavable site that is capable of being extended by an enzyme. Köster *et al.* does not teach or suggest the reduction in the length of nucleic acids prior to analysis by mass spectrometry. The reference does not teach or suggest incorporating chemical modifications into the primer to result in sites that permit reduction of molecular weight prior to analysis.

Richards *et al.* does not cure the defects in the teachings of Köster *et al.* Richards does not teach or suggest preparation of a primer with a chemically cleavable site specifically located in the 3'-end of the primer that is enzymatically extendable, and certainly does not suggest a primer with such a site located within about five nucleotides from the 3'-end of the primer (claim 2). As noted above, Richards *et al.* indicates that any modification is preferably located in the middle of a primer, and specifically teaches such modification and modifications at the 5'-end.

Neither Richards *et al.* nor Köster *et al.*, singly or in any combination thereof, teaches or suggests any of the specific requirements of the dependent claims. Neither teaches or suggests including a cleavable site 5 nucleotides from the 5'-end. Richards *et al.* does not teach or suggest a nucleic acid primer containing an immobilization attachment site or a solid support comprising an antibody.

Therefore, the combination of the teachings of Köster *et al.* and Richards *et al.*, which fails to teach or suggest preparation of an enzymatically extendable primer with a cleavage site in the 3'-region of the primer, does not result in the subject matter of the pending claims. Therefore, because the combination of teachings of the references does not result in the instantly claimed nucleic acid primers, the Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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